Autoimmune Disorders Advisory

Diagnosis/Condition:	Various Autoimmune Disorders
ICD-10 Codes:	D89.89
Origination Date:	01/2024
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CHP Advisories are designed to inform integrative healthcare providers on a range of clinical, diagnostic, and otherwise pertinent aspect of an evidence-based practice.

Evidence-based practice incorporates the best research evidence, clinical expertise, and patient preferences to guide clinical decision making. The Advisories have been developed from a combination of peer reviewed research evidence and clinical expertise, skills, and knowledge. Whenever possible, research literature is cited to support recommendations expressed in the Advisories. Clinical expertise and knowledge from practitioners in the fields of chiropractic, naturopathic medicine, acupuncture, and massage therapy are also incorporated to produce an apprised and pragmatic document. The reader is encouraged to evaluate the evidence and recommendations presented in these Advisories in the context of the unique characteristics, culture, and preferences of their patients and their own clinical knowledge.

Introduction

An autoimmune disorder (AD) is when the immune system attacks healthy body tissue 'by mistake' leading to, inflammation, cell injury, or functional changes manifesting with clinical signs/symptoms.[1] It is more accurately defined as, *"Autoimmunity that results over time in a pathological outcome with self-reactive, or autoreactive, B-cells, T-cells and autoantibodies causing tissue damage."*[2] Autoimmunity is when the immune system fails to distinguish 'self from non-self'.

The etiology of ADs is complex and although the exact mechanism is unknown it is evident that the disorders are influenced by genetic, hormonal and environmental factors.[3] Of note, while most ADs include inflammation not all inflammation is autoimmune.[4] Autoinflammatory disorders are rare, but do resemble ADs, with inflammation and multisystem manifestations. A key difference is the lack of a defined adaptive immune response, i.e. no autoantibodies (autoreactive T or B cells).[5] Examples of autoinflammatory disorders include: Bechet's Syndrome & Familial Mediterranean fever.

The scope and financial impacts of ADs is staggering. One estimates calculated ~$100 billion spent per year for medical costs in the US, making ADs the most expensive disease to treat.[6] As a whole, ADs include an estimated 80-150 chronic conditions that often lead to significant quality of life impairments.[7] One reason for the wide estimated range is due to differing approaches in characterization (clinical criteria or underlying biological mechanisms). Another reason is the lack of a national registry, leading to difficulty tracking incidence and prevalence. In 2022, this led to the NIH establishing the Office of Autoimmune Disease Research, with one aim of developing a more systematic method of collecting data.[8] Despite these limitations the prevalence of ADs in the US is estimated to be 7.6- 9.4%.[7] Other estimates, assessing ANA assays (frequent clinical screening tool) suggest an increasing prevalence: 11.0% (1988–1991) to 16.1% (2011–2012).[12] Global data also suggests ADs are increasing, alarmingly the estimated rate is ~12% annually.[9] This may be in part due to the expanding range of diseases; as new/additional disorders are found to have laboratory or clinical features implicating "autoimmune signatures".[10]

Some of the more common ADs are: celiac disease, diabetes (type 1), inflammatory bowel disease, multiple sclerosis, psoriasis, and rheumatoid arthritis.[11] Many conditions share hallmark symptoms (e.g. fatigue, malaise, joint pain) that may wax and wane over time.

History and Presentation

ADs represent a heterogeneous group of disorders that affect a specific tissue/organ and sometimes multiple systems. Despite their varied nature, there is a common cluster of symptoms including: fatigue, malaise, rashes, pain (joints), nausea, headaches, dizziness and more.[12] Evidence suggests the following risk-factors for the presence/development of ADs:

Gender
ADs are more common in women, with female-to-male ratios reaching 6:1 or higher for some diseases. [7]

Genetics
Evidence for inherited susceptibility is often present in families of patients with ADs.[7]

Pre-existing Conditions
Data suggests that AD is a risk factor to develop additional ADs. [7] In addition, it appears to increase the risk of developing cancer and cardiovascular disease.[13,14]

Environment
Mounting research supports a "second-hit" hypothesis, suggesting the influence of environmental exposure, more than genetics, shaping our immune system. Some key exposures associated with ADs are infectious agents and more prominently, environmental toxins (e.g., respirable silica or particulate matter).[4,7,10]

Socio-Economic Status & Stress
Mounting evidence suggests lower socio-economic status and traumatic stress increase the likelihood of developing ADs.[15-17] The influence of stress on the development of ADs has been assessed from the perspective of early influences, such as Adverse Childhood Events[15] and veterans with post-traumatic stress disorder (PTSD).[17]

Clinical presentation may include:

- Constitutional
    - Fever, weight loss, malaise, brain fog

- Musculoskeletal – arthralgias, arthritis, synovitis, myopathy.
    - Symmetrical emphasis
- Gastrointestinal – gastroesophageal reflux disease, abdominal pain, nausea
- Dermatologic – skin rashes, Raynaud phenomenon, photosensitivity
- Otorhinolaryngologic – sicca syndrome, oral ulcers
- Hematologic –iron deficient anemia

Insights from an Integrative Healthcare Lens

The current 'autoimmune tautology' hypothesis suggest that all ADs share a common pathophysiological mechanism *"…as a consequence of sharing genetic and environmental factors…"*.[18] Of note, the influence of environmental exposure is suggested as more impactful then genetics in shaping the immune system response.[10] Aspects of this theory are expanded into several categories that fall directly into the purview of Integrative Health Care (IHC). Specifically, the lifestyle impacts of: Environmental exposures (e.g. particulate matter), stress/mental health, diet (e.g. Ultra-processed food), and gut health (e.g. microbiome). A common aspect of IHC is the whole systems approach to care, often centered around digestive health and sense of wellbeing. When viewed through the lens of IHC, the hallmark symptom cluster (e.g., malaise, fatigue, pain, fever) can be indicative of ADs.

Listed below are four key 'exposure' themes that may be a common thread among the varied symptom patterns of the estimated 150 chronic conditions that are considered ADs:

Trauma

The incidence of Adverse Childhood Events (ACEs) suggested an increased risk of developing ADs; ≥2 ACEs led to a 70% increased risk for hospitalizations with Th1-type ADs (e.g. IBD, DM; n=15,357).[15] Evidence from a cohort of veterans (n=666,269) suggests that those diagnosed with PTSD were twice as likely to develop ADs (ARR = 2.00).[17]

Environmental/Oxidative Stress

One factor for the increasing global incidence of autoimmunity is environmental, such as exposure to toxic chemicals.[19] Indeed, environmental agent-mediated *oxidative stress (OS)* is pivotal in the pathogenesis of ADs; some estimates suggest a direct influence of ~70% of all ADs.[3] Some common factors that may lead to increased OS include exposure to: air pollution, pesticides, toxins, heavy metals, and radiation.[20]

Air pollutants and particulate matter are especially impactful and directly increase OS. A population based cohort (n=81,363) found that chronic exposure to traffic and industrial derived pollutants was associated with an increased risk of developing ADs; most notable for three key areas: *1)* Rheumatoid arthritis (40% increase); 2) Inflammatory bowel disease (20%); 3) Connective tissue disorders (15%).[21]

Lifestyle/ Diet Related
Some common lifestyle mediated factors that may lead to increased oxidative stress include: obesity, smoking, excess alcohol, excess sunlight exposure, and poor diet.[20]

Proinflammatory Foods: Dietary effects vary among ADs, however, guidelines suggests that avoidance of proinflammatory foods (e.g. red meat and sugar-sweetened beverages), are associated with improved outcomes for many conditions.[7]

- UPFs: A dietary aspect gaining attention is the increased consumption of Ultra-processed foods (UPFs)[22]. Studies suggest that diets high in these are associated with increased risk of autoimmune disease.[23] UPFs are also suggested to negatively alter the microbiome.[22]

- Omega-3: Diets supplemented with 1g of marine-based omega-3 fatty acids demonstrate a protective effect for ADs at longer-term follow-up (2-4years).[24,25]

A note on Microbiome Effects
There is emerging evidence of the influence our gut microbiota play in the development of ADs. For example, abnormalities of the microbial community, (dysbiosis), is observed in patients with autoimmune diseases.[26] However, it remains uncertain whether microbiome is a causative factor or a consequence.[3] Despite the uncertainty, microbiota-targeted strategies are evolving, such as probiotics and fecal microbiota transplantation for the treatment of type 1 diabetes, multiple sclerosis, and rheumatoid arthritis.[26]

Assessment
It is recommended to collect personal and family medical history and if needed a symptom tracking journal. Perform a thorough physical exam with specific body systems depending on the symptoms. Diagnosis is difficult due to the variety and variability of ADs; consult with a specialist or refer based on primary clinical concerns.

Examples of key diagnostic laboratory tests include:
- Antinuclear antibody tests (ANA) & RF
- Autoantibody tests (specific to the condition)
- Complete blood count (CBC)
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR)
- Comprehensive metabolic panel (CMP)
- Organ function tests and/or imaging (depending on symptoms

Differential Diagnosis

While most ADs include inflammation, these must be distinguished from autoinflammatory disorders. These disorders resemble autoimmune diseases, with inflammation and multisystem manifestations, but lack a defined adaptive immune response (no autoreactive T or B cells).[5]

Clinical manifestation should be evident in addition to the presence of autoantibodies. [4] Although often the first step in diagnoses, autoantibodies are not sufficient; may not be the mediators of disease (can occur non-specifically). See referral guideline below.

When to Refer:	Abnormal labs panel may lead to referral. Note: Autoantibodies may be present for years before the diagnosis of disease. (Identify the stopping point for conservative care and indications for referral.) Emergency referral for any suspected life-threatening conditions such as myocarditis, stroke, or renal failure. Patients with symptoms lasting more than 3 months. Consider the hallmark symptoms that often wax and wane over time, (e.g., fatigue, malaise, joint pain) and 'exposure' themes (e.g. *Trauma, Environmental exposures, & Lifestyle/Diet)*
Specialty:	PCP or subspecialty relevant to specific symptoms as needed (e.g, rheumatology, neurology)
Other Considerations:	For patients with family history (1st degree relative) consider immediate referral; no need to wait 3mths

Resources for Clinicians*

- NIH Office of Autoimmune Disease Research: https://orwh.od.nih.gov/OADR-ORWH
- Autoimmune Institute: https://www.autoimmuneinstitute.org/effective-communication-strategies/
- Enhancing NIH Research on Autoimmune Disease: https://nap.nationalacademies.org/catalog/26554/enhancing-nih-research-on-autoimmune-disease
- Autoinflammatory Diseases Basics (NIH): https://www.niams.nih.gov/health-topics/autoinflammatory-diseases/basics/symptoms-causes

Resources for Patients*

- MedLine Plus (National Library of Medicine): https://medlineplus.gov/autoimmunediseases.html
- Autoimmune Institute: https://www.autoimmuneinstitute.org/understanding-autoimmune-disease/

*Health Disparities/Inequities, Caveats to Race-Based Medicine, and Related Resources

- It is recognized that unequal distribution of resources (e.g. environmental, economic) and other social determinants of health (e.g. employment, housing) are root causes of health disparities and differences of health status in racial, ethnic, and other groups.[27,28] When a study attributes race to a difference in prevalence of a disease or clinical outcome or presentation, it should be understood that race is a social construct and genetic or biologic interpretations of race are not supported by science. Indeed, the Human Genome Project demonstrated that on average, humans are 99.9% identical at the DNA level; there is more genetic variation within 'races' than between them.[29]
- CDC: https://www.cdc.gov/healthequity/racism-disparities/index.html
- NIH: https://www.training.nih.gov/2020_inclusion_anti-racism_and_wellness_resources
- OHSU: https://www.ohsu.edu/center-for-diversity-inclusion/anti-racist-resources
- Seattle: https://providernews.seattlechildrens.org/anti-racism-resources-for-healthcare-professionals/

Clinical Advisory Feedback

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Clinical Services Department: cs@chpgroup.com

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